REMARKS

I. Status of the Application and Claims

Claims 17-29 are pending. Applicants acknowledge and appreciate the Office's withdrawing of the restriction requirement and agreeing to examine all pending claims. Office Action, page 2.

Applicants have amended claims 17 and 18 solely to more particularly describe the subject matter claimed therein. Support for the claim amendments is found in the application as filed. For example, embodiments of the invention comprising a "at least one pharmaceutically acceptable vehicle" are found at page 31, lines 15-17. Also, for example, page 7, lines 5-6, describe an amino group that is optionally substituted with a methyl group. No new matter has been added.

II. Objection to Claim 26

The Office has objected to claim 26 because the claim ends in a comma rather than a period. *Id.* Applicants have amended the claim so that it ends in a period. They respectfully request withdrawal of the objection.

III. Rejections Under 35 U.S.C. § 112

Claims 17-29 have been rejected as allegedly indefinite under 35 U.S.C. § 112, second paragraph. *Id.*, page 3.

The Office alleges that claim 17 is indefinite because the Office cannot determine whether the claim should be read "as a composition comprising 1) an acid sensitive compound comprising, a) the ortho ester, and b) a hydrophilic substituent." *Id.* Applicants have amended claim 17 so that the components of the composition are defined as components "(a)" and "(b)".

The Office also alleges that claim 17 is indefinite because it allegedly "comprises only one active agent" and that a "composition must contain more than 1 agent, otherwise what is claimed is not a composition, but a compound." *Id.* The Office states that "[a]dding an additional additive to the composition will obviate this rejection." *Id.* Applicants have amended claim 17 so that it recites the additional additive of "at least one pharmaceutically acceptable vehicle".

Claims 17 and 18 are rejected as indefinite for reciting "an amino group that is optionally substituted" without specifically reciting "the identity of the moieties which are intended to be substituted...." *Id.*, pages 3-4. Applicants disagree and traverse the rejection because one of ordinary skill in the art would understand which moieties may be substituted on the amino group. Solely to advance prosecution, however, Applicants have amended claims 17 and 18 to recite "an amino group that is optionally substituted with a methyl group."

Claim 18 is allegedly indefinite for reciting "a steroid derivative." *Id.*, page 4. Applicants disagree and traverse the rejection because one of ordinary skill in the art reading the specification would understand the meaning of "a steroid derivative." For example, the specification provides a definition of the term "steroid derivative" for the purposes of the invention at page 11, line 26, to page 12, line 7. "When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning...." *See* M.P.E.P § 2173.05(a).

Claim 19 is allegedly indefinite for reciting "a biologically active substance." *Id.* Applicants disagree and traverse the rejection because one of ordinary skill in the art reading the specification would understand the meaning of "a biologically active

substance." For example, the specification provides a definition of the term "biologically active substance" for the purposes of the invention at page 16, lines 10-11.

Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Rejections Under 35 U.S.C. § 103(a)

Claims 17-29 have been rejected under 35 U.S.C. § 103(a) as being obvious over the combination of U.S. Patent No. 6,200,599 B1 to Nantz ("Nantz") and Rodrigues *et al.*, "Acid Sensitive Polyethylene Glycol Conjugates of Doxorubicin: Preparation, In Vitro Efficacy and Intracellular Distribution," Bioorganic and Medicinal Chemistry, 7:2517-2524 (1999) ("Rodrigues"). Office Action, pages 4-9. Applicants traverse this rejection.

To establish a *prima facie* case of obviousness, the Office must demonstrate that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or combine reference teachings. In addition, the Office must demonstrate that one of ordinary skill in the art would have a reasonable expectation of success of combining the cited references to arrive at the claimed invention. *See* M.P.E.P. § 2143. Furthermore, the teaching or suggestion to make the claimed modification must be found in the prior art, not in Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). In the present case, the Office has failed to make a *prima facie* case of obviousness because it has not met either, let alone both, of the above criteria.

No Motivation to Combine the References

The suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999 (Fed. Cir. 1999). Thus, while a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the prior art, that modification is not obvious unless the prior art suggested the desirability of such a modification. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). Furthermore, the Office has the burden to provide some objective evidence, not found in the Applicants' specification, or reasoned argument showing that one of ordinary skill in the art would have been motivated to combine the prior art to devise the claimed invention. *In re Lee*, 277 F.3d 1338, 1433 (Fed. Cir. 2002).

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness because there simply is no clear and particular suggestion in the cited references to combine the amphipathic liposome-forming ortho ester lipids of Nantz with Rodrigues' water-soluble polyethylene glycol (PEG) conjugates to devise the claimed invention.

Nantz's ortho ester lipids of formula (I) are disclosed as containing "a hydrophilic domain or head group." Col. 3, lines 21-24, and Figure 1(E). This hydrophilic domain or head group is defined in Nantz's formula (I) as

> a nitrogen containing head group wherein the nitrogen can be unsubstituted, mono-substituted, di-substituted, or a quaternary nitrogen salt and wherein the nitrogen substituent(s) include, but are not limited to, optionally substituted (C1-C18_alkyl, optionally substituted (C2-C18)alkenyl, and optionally substituted (C2-C18)alkynyl and wherein R4 and Q are optionally linked with a (C1-C5)alkylene or (C2-C5) alkenyl group.

Col. 3, lines 10-18. The Office admits that Nantz does not teach using "a polyalkylene glycol as the hydrophilic group nor to add a vehicle for topical and/or injectable formulations". Office Action, page 8.

Rodrigues discloses water-soluble-PEG/doxorubicin conjugates "designed to increase the water-solubility and plasma half-life of the drug while slowly releasing the parent compound through hydrolysis of the chemical link between the drug and the polymer backbone". P. 2517, first paragraph. Rodrigues uses an acid sensitive hydrazone linker between the PEG and doxorubicin, wherein acid induced hydrolysis of this linker results in release of doxorubicin from the PEG moiety. P. 2519. The Office concludes

> One would be motivated to use the polyethylene glycol [of Rodrigues] as the hydrophilic head group [in Nantz's ortho ester lipid] as Rodrigues et al. teaches that a PEG-drug complex is also a complex which requires an acid induced drug releasing mechanism thus providing a liposome complex which would break-down in an acidic environment, ultimately releasing its active agent.

Office Action, pages 8-9. Applicants disagree.

Applicants submit that the Office has provided no objective evidence or reasoned argument for it's conclusory statement that one would be motivated to use Rodrigues' polyethylene glycol as the hydrophilic head group in Nantz's ortho ester lipid liposomes. Rodrigues' PEG moiety provides an "increase the water-solubility and plasma half-life of the drug." P. 2517, first paragraph. The combination of references and arguments of record do not teach or suggest that Rodrigues' water-soluble-PEG/doxorubicin conjugates can self-assemble into liposome form as required by Nantz. Similarly, there is no objective evidence or reasoned argument of record that Rodrigues' water-soluble-PEG moiety is useful for forming self-assembled liposomes as required by Nantz.

Accordingly, the Office has not met its burden of providing objective evidence or reasoned argument that Rodrigues' PEG moiety is useful a head group in Nantz's ortho ester lipid.

Also, the Office provides no objective evidence or reasoned argument that Rodrigues' water-soluble-PEG would make a suitable structural replacement for Nantz's hydrophilic head group as specifically defined in R4 of Nantz's formula (I). It is known in the art that the ability of amphipathic molecules to self-assemble into macromolecular structures, such as liposomes, depends in part on "the relative sizes of the hydrophilic and hydrophobic regions of the molecule." Nantz, Col. 1, lines 1-42. Applicants point out that Nantz specifically defines their hydrophilic head group as a "nitrogen containing head group" that in some circumstances may be tri-substituted with three C18 alkyl groups. Col. 3, lines 10-16. An R4 head group might thereby have a molecular size in the range of about 700-1000 D. Rodrigues PEG moieties range in size from 20,000-70,000 D. Applicants submit that one of ordinary skill in the art would not have been motivated to replace Nantz's 1,000 D nitrogen containing hydrophilic head group with Rodrigues' 20,000-70,000 D PEG moiety, because such a substitution would have significantly altered the relative sizes of the hydrophilic and hydrophobic regions of Nantz' ortho ester lipid, and Nantz method required self-assembly of a particular a macromolecular liposome structure that is dependent on the relative sizes of the hydrophilic and hydrophobic regions of the ortho ester lipid for self assembly to occur.

To support it's conclusory statement that one would be motivated to use Rodrigues' PEG as the hydrophilic head group in Nantz's ortho ester lipid liposomes, the Office alleges that both molecules provide the same ultimate function, acid induced

release of an active agent, by using similar structural features: an acid sensitive linker, a hydrophilic group, and acid induced release of the hydrophilic group. Because of these allegedly similar functional and structural characteristics, the Office erroneously concludes that one would have been motivated to replace a structural element of Nantz (hydrophilic head group) with the structural element of Rodrigues (hydrophilic PEG moiety) and still retain the function sought for in Nantz. Applicants, however, point out the Office's erroneous assumptions. The release of active agent proceeds by using two very different structural paradigms for each method.

Acid induced hydrolysis of the Rodrigues PEG-drug compound hydrolyzes the covalent bond linking the active agent to the vehicle molecule, PEG. In Rodrigues, the active agent is released instantaneously in a hydrolysis single step. Thus, a single PEG moiety performs the function of delivery vehicle. Rodrigues' PEG moiety allows for stable delivery of the active agent to a target environment, upon reaching the target the PEG does not participate in the release of the active agent. The structural properties of Rodrigues' hydrophilic PEG moiety do not contribute to the mechanism of release of the active agent.

Acid induced hydrolysis of the Nantz ortho ester lipid hydrolyzes the covalent bond linking structural components, the released structural components then act to destabilize the self-assembled structural organization of the liposomes, and disassembly of the liposomes results in release of active agent encapsulated by the liposome. In Nantz, the active agent is released only after a multi-step process following acid induced hydrolysis, and the active agent is not covalently linked to the liposome vehicle. In Nantz, neither a single ortho ester lipid nor its head group

functions as delivery vehicle of active agent. Unlike Rodrigues' molecule, the structural properties of Nantz's hydrophilic head group moiety contributes to the release of the active agent.

Accordingly, Applicants submit that one would not be motivated to substitute Nantz's hydrophilic head group with Rodrigues' PEG moiety because they perform different functions in their respective methods. Rodrigues' PEG moiety functions as a hydrophilic delivery vehicle of the active agent, and does not participate in the release of the active agent. In contrast, Nantz's hydrophilic head group functions as a unit component stabilizing macromolecular liposome structure, and does participate in the structural release of the active agent from the liposome vehicle. Applicants submit that the Office has not provided objective evidence or reasoned argument indicating that Rodrigues' 20,000-70,000 D PEG moiety would function as a unit component stabilizing macromolecular liposome structure, and would participate in the structural release of the active agent from the liposome vehicle if it replaced Nantz's <1000 D hydrophilic nitrogen containing headgroup

For any of the reasons above, and according to the standard set forth in *In re Lee*, the Office's conclusory statements that there is motivation to use Rodrigues' PEG moiety in place of Nantz's hydrophilic nitrogen containing headgroup are not sufficient for showing a motivation to combine the references and therefore do not support a *prima facie* case of obviousness.

Applicants respectfully request that the Office reconsider and withdraw the rejection.

No Reasonable Expectation of Success

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success of combining the cited references to arrive at the claimed invention. M.P.E.P. § 2143. Applicants submit that there is no reasonable expectation of success of combining Nantz and Rodrigues to arrive at the claimed invention.

Applicants submit that the Office's suggested replacement of Nantz's nitrogen containing hydrophilic head group (<1,000 D) with Rodrigues' bulky (20,000-70,000 D) water-soluble PEG moiety is unpredictable at best, and may in fact prevent Nantz's liposomes from forming. It is known in the art that the ability of amphipathic molecules to self-assemble into macromolecular structures, such as liposomes, depends in part on "the relative sizes of the hydrophilic and hydrophobic regions of the molecule." Nantz, Col. 1, lines 1-42. Applicants point out that Nantz specifically defines their hydrophilic head group as a "nitrogen containing head group" that in some circumstances may be at most tri-substituted with three C18 alkyl groups. Col. 3, lines 10-16. An R_4 head group might thereby have a molecular size ranging up to about 700-1000 D. Rodrigues PEG moieties range in size from 20,000-70,000 D. Applicants submit that, without further experimentation with liposome compositions, one of ordinary skill in the art would not have had had a reasonable expectation of success practicing Nantz's method of replacing Nantz's <1,000 D nitrogen containing hydrophilic head group with Rodrigues' 20,000-70,000 D PEG moiety, because such a substitution would have significantly altered the relative sizes of the hydrophilic and hydrophobic regions of Nantz' ortho ester lipid, and Nantz method required self-assembly of a particular a macromolecular

liposome structure that is dependent on the relative sizes of the hydrophilic and hydrophobic regions of the ortho ester lipid for self assembly to occur.

For this reason as well, Applicants respectfully request that the Office reconsider and withdraw the rejection.

SUMMARY

In view of the above amendments and remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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